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Extended Summaries SCI Pesticides Group Meeting Design of Bioactive Compounds

The following are extended summaries based on posters presented at the meeting 'Design of Bioactive Compounds: Possibilities for Industrial Applications' organised by R. Greenwood, M. Ford, R. Francke and R. Rees on behalf of the SCI Pesticides Group and held on 4–7 September 1995 at Hotel Residence, Potsdam, Germany. They are entirely the responsibility of the authors and do not necessarily represent the views of the Editorial Board of Pesticide Science.

Design of Active Analogues of a Peptide Using D-optimal Design, QSAR Models and a Combinatorial Search Algorithm

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A novel set of algorithms and computational tools has been developed within PROMETHEUS™ a comprehensive computational environment for molecular modelling, design and simulation. These have been developed for the design of peptide analogue sets from a single lead and have been applied to optimise the potency of a 15-residue peptide. The chosen lead peptide, CAMELO, was designed in the laboratory of Boman.[1–5] It is a hybrid of cecropin A, a 37-residue antimicrobial peptide produced by silk moth larvae, and melittin, a 26-residue peptide extracted from bee venom, and combines to some extent the cytolytic activity of melittin while retaining the selectivity of cecropin A for prokaryotic cells. Our objective was to test analogues of CAMELO and to find alternative sequences with increased potency against a panel of bacterial strains.

The physicochemical properties of the molecules were described by the residue-based parameters of Hellberg and co-workers (Z scales)[6] and Norinder (ID Scales)[7] and covariance functions derived from these (Table 1). A third group of descriptors, referred to as the 'Design parameters', represent particular molecular properties which have been suggested as relevant to structure–activity relationships for this class.

A D-optimal design[8] in the Principal Components sub-space of these descriptors produced a QSAR training set of 60 molecules well distributed in the possible design space for 15mer peptides.

The antibacterial potencies of the peptides were assayed and shown to be well spread in activity space. Partial Least Squares (PLS) analysis was used to develop a variety of QSAR models. The best model identified had a cross-validated R^2 value = 0.65. Descriptors based on covariances of the Z-scales appeared to provide the most predictive model of the training set data, and with this data set, they performed better than the Norinder scales. The covariance scales were calculated using similar methods to Wold *et al.*[9] Like them, we found that the covariance parameters gave an improved model of the data, which may be

TABLE 1

Model	*Cross-validated* R^2
Z scales	0·44 (2 lv)[a]
Z scale covariances	0·65 (lag 8, 6 lv)[b]
ID scales	0·42 (2 lv)
ID scale covariances	0·35 (lag 6, 1 lv)
Design parameters	0·50 (1 lv)

[a] lv = Number of latent variables in PLS model.
[b] lag = Maximum lag used to calculate covariance terms.

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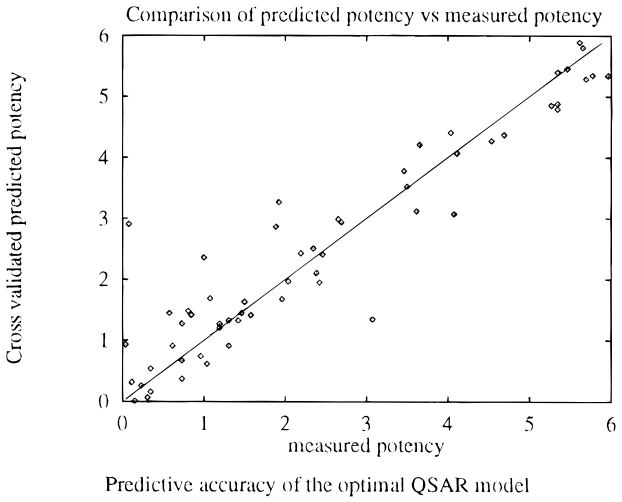

Fig. 1. Predictive accuracy of the optimal QSAR model.

because the covariance scales are much less dependent on the sequence alignment. Model predictions of potency of the compounds in the training set are shown in Fig. 1. Predictions were generated using leave-one-out cross-validation. The logarithmic potency scale used here measures average activity against the panel of bacteria. A unit increase in potency represents a two-fold reduction in the geometric mean MIC.

New sequences were generated by a combinatorial search algorithm. At each round all possible single mutation analogues were evaluated using the best QSAR model. Initially the most potent peptides were used as seeds, those with the highest predicted potencies being used in subsequent rounds. New peptides generated by this process have been assayed and shown to have high potency. A more detailed description of the search algorithm and the results obtained is given in Mee *et al.*[10]

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BIOSTER—A Database of Structurally Analogous Compounds

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To aid the discovery of new drugs and agrochemicals, a compilation of critically selected molecule pairs with similar structures and biological activities is being

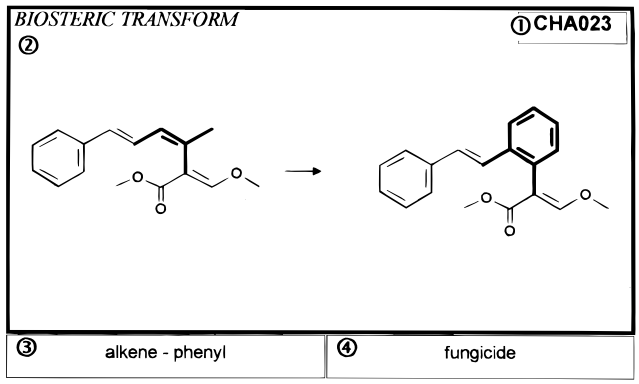

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Fig. 1. Typical data form of *BIOSTER* database with field types as follows: ① ID code; ② structures of the biosteric transformation (biosteric fragments in the analogues are highlighted); ③ chemical fragment types relevant to transformation; ④ biological activity type related to the structures shown; ⑤ key references.